Amendments to the CLAIMS

Applicant submits below a complete listing of the current claims, including marked-up claims with insertions indicated by underlining and deletions indicated by strikethroughs and/or double bracketing. This listing of claims replaces all prior versions, and listings, of claims in the application:

1. (original) A pharmaceutical preparation comprising a solution of methylnaltrexone or a salt thereof, wherein the preparation after autoclaving has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation.

2-6. (canceled)

7. (original) The pharmaceutical preparation of claim 1, wherein the pharmaceutical preparation further comprises a chelating agent.

8. (original) The pharmaceutical preparation of claim 7, wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA) or a derivative thereof.

9. (canceled)

10. (original) The pharmaceutical preparation of claim 8, wherein the EDTA or derivative thereof is present in a concentration ranging from 0.001 to 100.0 mg/ml.

11-16. (canceled)

17. (original) The pharmaceutical preparation of claim 1, further comprising a buffering agent.

18. (original) The pharmaceutical preparation of claim 17, wherein the buffering agent is citrate buffer.

19. (original) The pharmaceutical preparation of claim 18, wherein the citrate is present in a concentration ranging from 0.01 to 100.0 mM.

20–21. (canceled)

22. (Previously amended) The pharmaceutical preparation of claim 1, wherein the pH of the preparation does not exceed 4.25.

23–25. (canceled)

26. (Previously amended) The pharmaceutical preparation of claim 1, wherein the concentration of methylnaltrexone ranges from 0.01 to 100 mg/ml.

27–32. (canceled)

33. (Previously amended) The pharmaceutical preparation of claim 1, further comprising an anti-oxidant.

34. (Previously amended) The pharmaceutical preparation of claim 1, further comprising an isotonicity agent.

35. (Previously amended) The pharmaceutical preparation of claim 1, further comprising an opioid.

36. (Previously amended) The pharmaceutical preparation of claim 1, further comprising a cryoprotective agent.

37. (original) The pharmaceutical preparation of claim 36, wherein the cryoprotective agent is a polyol.

38. (Previously amended) The pharmaceutical preparation of claim 1, wherein the solution is provided in a vial or ampoule with a septum.

39. (Previously amended) The pharmaceutical preparation of claim 1, wherein the solution is provided in a syringe, infusion bag or sealable bottle.

40–43. (canceled)

44. (Previously amended) The pharmaceutical preparation of claim 1, wherein the solution is provided in a container including indicia indicating that the pharmaceutical preparation has been autoclaved.

45–49. (canceled)

50. (original) A method for preparing an autoclaved pharmaceutical preparation that has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation comprising:

providing a solution having a pH of 4.25 or less comprising methylnaltrexone or salt thereof and being substantially free of methylnaltrexone degradation products; and

autoclaving the solution.

51–53. (canceled)

54. (Previously amended) The method of claim 50, wherein the solution contains a chelating agent.

55. (Previously amended) The method of claim 50, wherein the solution further comprises an isotonicity agent.

56. (Previously amended) The method of claim 50, wherein the solution comprises a buffering agent.

57. (canceled)

58. (Previously amended) The method of claim 50 wherein the solution comprises an anti-oxidant.

59–60. (canceled)

61. (original) The method of claim 54, wherein the chelating agent is EDTA or derivative thereof.

62. (original) The method of claim 56, wherein the buffering agent is citrate buffer.

63. (Previously amended) The method of claim 50 further comprising lyophilizing the solution.

64. (original) The method of claim 63, further comprising adding a cryoprotecting agent to the solution.

65. (original) The method of claim 63, wherein the cryoprotective agent is a polyol.

66. (original) A method for preparing an autoclaved pharmaceutical preparation that has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation comprising:

providing a solution comprising methylnaltrexone or salt thereof and a chelating agent, the solution being substantially free of methylnaltrexone degradation products; and

autoclaving the solution.

67. (original) The method of claim 66, wherein the chelating agent is EDTA or derivative thereof.

68. (original) The method of claim 67, wherein the EDTA or derivative thereof is present in a concentration ranging from 0.001 to 100.0 mg/ml.

69–70. (canceled)

71. (Previously amended) The method of claim 66 wherein the solution contains a buffering agent.

72. (original) The method of claim 71, wherein the buffering agent is citrate buffer.

73. (original) The method of claim 66, wherein the solution is adjusted to have a pH of 4.25 or less.

74–76. (canceled)

77. (original) The method of claim 66, wherein the solution contains an anti-oxidant.

78. (original) The method of claim 66, wherein the solution contains an isotonicity agent.

79–82. (canceled)

83. (original) The method of claim 66, further comprising lyophilizing the solution.

84. (original) The method of claim 83, further comprising adding a cryoprotecting agent to the solution.

85. (original) The method of claim 84, wherein the cryoprotective agent is a polyol.

86. (original) A pharmaceutical preparation comprising a solution of methylnaltrexone or a salt thereof, wherein the preparation after storage at about room temperature for six months has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone in the preparation.

87–91. (canceled)

92. (Previously amended) The pharmaceutical preparation of claim 86, wherein the pharmaceutical preparation further comprises a chelating agent.

93. (original) The pharmaceutical preparation of claim 92, wherein the chelating agent is EDTA or derivative thereof.

94. (original) The pharmaceutical preparation of claim 93, wherein the EDTA or derivative thereof is present in a concentration ranging from 0.001 to 100.0 mg/ml.

95–100. (canceled)

101. (original) The pharmaceutical preparation of claim 86, wherein the pharmaceutical preparation further comprises a buffering agent.

102. (original) The pharmaceutical preparation of claim 86, wherein the buffering agent is citrate buffer.

103. (original) The pharmaceutical preparation of claim 102, wherein the citrate is present in a concentration ranging from 0.01 to 100.0 mM.

104-105. (canceled)

106. (Previously amended) The pharmaceutical preparation of claim 86, wherein the pH does not exceed 4.25.

107–109. (canceled)

110. (Previously amended) The pharmaceutical preparation of claim 86, wherein the concentration of methylnaltrexone ranges from 0.01 to 100 mg/ml.

111-116. (canceled)

117. (Previously amended) The pharmaceutical preparation of claim 86 further comprising an anti-oxidant.

118. (Previously amended) The pharmaceutical preparation of claim 86, further comprising an isotonicity agent.

119. (Previously amended) The pharmaceutical preparation claim 86, further comprising a cryoprotective agent.

120. (original) The pharmaceutical preparation of claim 119, wherein the cryoprotective agent is a polyol.

121. (Previously amended) The pharmaceutical preparation of claim 86, further comprising an opioid.

122-128. (canceled)

129. (original) The pharmaceutical preparation of claim 86, wherein the solution is provided in a vial or ampoule with a septum, in a syringe, an infusion bag, or a sealable bottle.

130–132 (canceled)

133. (original) The pharmaceutical preparation of claim 86, wherein the solution is provided in a container including indicia indicating that the solution has been autoclaved.

134-135. (canceled)

136. (original) A stable pharmaceutical preparation comprising a solution of methylnaltrexone or salt thereof, wherein the pH is below 4.25.

137–139. (canceled)

140. (Previously amended) The pharmaceutical preparation of claim 136 wherein the pH is adjusted with an acid selected from the group consisting of HCl, citric acid, sulfuric acid, acetic acid, or phosphoric acid.

141. (Previously amended) The pharmaceutical preparation of claim 136 wherein the preparation further comprises a buffering agent.

142. (original) The pharmaceutical preparation of claim 141, wherein the buffering agent is selected from the group consisting of citric acid, sodium citrate, sodium acetate, acetic acid, sodium phosphate and phosphoric acid, sodium ascorbate, tartartic acid, maleic acid, glycine, sodium lactate, lactic acid, ascorbic acid, imidazole, sodium bicarbonate and carbonic acid, sodium succinate and succinic acid, histidine, and sodium benzoate and benzoic acid.

143. (original) The pharmaceutical preparation of claim 141, wherein the buffering agent is a citrate buffer.

144. (original) The pharmaceutical preparation of claim 143, wherein the citrate buffer concentration ranges from 0.001 mM to 100 mM.

145–146. (canceled)

147. (original) The pharmaceutical preparation of claim 136, further comprising a chelating agent.

148. (canceled)

149. (Previously amended) The pharmaceutical preparation of claim 147, wherein the chelating agent is selected from the group consisting of EDTA and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives sodium desoxycholate and derivatives thereof.

150–154. (canceled)

155. (Previously amended) The pharmaceutical preparation of claim 136 wherein the preparation is substantially free of methylnaltrexone degradation products.

156–157. (canceled)

158. (Previously amended) The pharmaceutical preparation of claim 136, wherein the pharmaceutical preparation has been autoclaved and the concentration of methylnaltrexone degradation products is less than 2.0% of the methylnaltrexone in the preparation.

159–162. (canceled)

163. (Previously amended) The pharmaceutical preparation of claim 136, wherein the methylnaltrexone or salt thereof is present in an amount effective to treat a side effect associated with opioid treatment when administered to a human subject.

164. (original) The pharmaceutical preparation of claim 163, wherein the concentration of methylnaltrexone or salt thereof is sufficient to treat constipation.

165. (Previously amended) The pharmaceutical preparation of claim 136, wherein the concentration of methylnaltrexone or salt thereof ranges from 0.01 to 100 mg/ml.

166–171. (canceled)

172. (original) The pharmaceutical composition of claim 141, further comprising an isotonicity agent.

173–175. (canceled)

176. (Previously amended) The preparation of claim 136, further comprising an antioxidant.

177–178. (canceled)

179. (original) The preparation of claim 176, wherein the antioxidant is selected from the group consisting of an ascorbic acid derivative, butylated hydroxy anisole, butylated hydroxy toluene, alkyl gallate, sodium meta-bisulfite, sodium bisulfite, sodium dithionite, sodium thioglycollic acid, sodium formaldehyde sulfoxylate, tocopherol and derivatives thereof, monothioglycerol, and sodium sulfite.

180. (Previously amended) The preparation of claim 136, further comprising a cryoprotective agent.

181–182. (canceled)

183. (original) The preparation of claim 180 wherein the cryoprotective agent is a polyol.

184. (Previously amended) The preparation of claim 136 further comprising an opioid.

185–186. (canceled)

187. (original) The preparation of claim 184, wherein the opioid is selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol.

188. (original) A stable pharmaceutical preparation comprising a solution of methylnaltrexone or salt thereof, wherein the solution further comprises a chelating agent in an amount sufficient to inhibit degradation of the methylnaltrexone or salt thereof, whereby the amount is such that the preparation after autoclaving has a concentration of methylnaltrexone degradation products that does not exceed 0.5 % of the methylnaltrexone or salt thereof in the preparation.

189. (original) The pharmaceutical preparation of claim 188, wherein the chelating agent is selected from the group consisting of EDTA and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, and sodium desoxycholate and derivatives thereof.

190–194. (canceled)

195. (Previously amended) The pharmaceutical preparation of claim 188 wherein the preparation further comprises a buffering agent.

196. (original) The pharmaceutical preparation of claim 195, wherein the buffering agent is selected from the group consisting of citric acid, sodium citrate, sodium acetate, acetic acid, sodium phosphate and phosphoric acid, sodium ascorbate, tartartic acid, maleic acid, glycine, sodium lactate, lactic acid, ascorbic acid, imidazole, sodium bicarbonate and carbonic acid, sodium succinate and succinic acid, histidine, and sodium benzoate and benzoic acid.

197-201. (canceled)

202. (original) The pharmaceutical preparation of claim 188, wherein the preparation is substantially free of methylnaltrexone degradation products.

203-205. (canceled)

206. (original) The pharmaceutical preparation of claim 188, wherein the methylnaltrexone or salt thereof is present in an amount effective to treat a side effect associated with opioid treatment when administered to a human subject.

207. (original) The pharmaceutical preparation of claim 206, wherein the concentration of methylnaltrexone or salt thereof is sufficient to treat constipation.

208. (original) The pharmaceutical preparation of claim 188, wherein the concentration of methylnaltrexone or salt thereof ranges from 0.01 to 100 mg/ml.

209-213. (canceled)

214. (original) The pharmaceutical composition of claim 188, further comprising an isotonicity agent.

215. (canceled)

216. (original) The composition of claim 214, wherein the isotonicity agent is selected from the group consisting of sodium chloride, mannitol, lactose, dextrose, glycerol, and sorbitol.

217. (canceled)

218. (canceled)

219. (original) The preparation of claim 188, further comprising an antioxidant.

220. (canceled)

221. (original) The preparation of claim 219, wherein the antioxidant is selected from the group consisting of an ascorbic acid derivative, butylated hydroxy anisole, butylated hydroxy toluene, alkyl gallate, sodium meta-bisulfite, sodium bisulfite, sodium dithionite, sodium thioglycollic acid, sodium formaldehyde sulfoxylate, tocopherol and derivatives thereof, monothioglycerol, and sodium sulfite.

222. (canceled)

223. (Previously amended) The preparation of claim 188 further comprising a cryoprotective agent.

224. (canceled)

225. (original) The preparation of claim 188, further comprising an opioid.

226. (canceled)

227. (canceled)

228. (original) The preparation of claim 225, wherein the opioid is selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol.

229. (canceled)

230. (canceled)

231. (Currently amended) A pharmaceutical preparation comprising a solution of methylnaltrexone or salt thereof and ~~at least one methylnaltrexone degradation inhibiting agent selected from the group consisting of~~ a chelating agent~~, a buffering agent, an antioxidant, and combinations thereof,~~ wherein the solution has a pH ~~ranging~~ from 2 to 6~~, wherein the degradation inhibiting agent is present in an amount sufficient to render the preparation stable, wherein the preparation is processed under at least one sterilization technique, and wherein the preparation is substantially free of methylnaltrexone degradation products~~.

232. – 246. (canceled)

247. (original) A method of inhibiting formation of methylnaltrexone degradation products in a pharmaceutical preparation comprising methylnaltrexone or salts thereof, the method comprising:

preparing an aqueous solution comprising at least one methylnaltrexone degradation inhibiting agent selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof;

dissolving a powdered source of methylnaltrexone or salt thereof with the solution to form the pharmaceutical preparation.

248-251. (canceled)

252. (original) The method of claim 247, further comprising adjusting with an acid the pH of the solution or the preparation to a pH ranging from 2 to 6.

253. (canceled)

254. (canceled)

255. (original) The method of claim 247, further comprising adding an isotonicity agent to the solution.

256. (original) A method of preparing a stable pharmaceutical preparation comprising an aqueous solution of methylnaltrexone or salts thereof to inhibit formation of methylnaltrexone degradation products, comprising:

providing a solution comprising methylnaltrexone or salts thereof and at least one methylnaltrexone degradation inhibiting agent;

processing the solution under at least one sterilization technique prior to and/or after terminal filling the solution in a sealable container to form the stable pharmaceutical preparation, wherein the method is carried out without the addition of a pH-adjusting-base to the solution.

257. (original) The method according to claim 256, wherein the concentration of methylnaltrexone degradation products is less than 2.0% of the total methylnaltrexone in the preparation.

258-260. (canceled)

261. (original) The method of claim 256, wherein the methylnaltrexone degradation inhibiting agent is selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof.

262-266. (canceled)

267. (Previously amended) The method of claim 256 wherein the initial solution is adjusted to a pH ranging from 2 to 6 prior to the processing under the at least one sterilization technique.

268-270. (canceled)

271. (original) The method of claim 256, wherein the aseptic technique is autoclaving after terminal filling the sealable container.

272. (original) The method of claim 256, wherein the processing comprises sterile filtration prior to terminal filling followed by autoclaving after terminal filling the sealable container.

273. (original) The method of claim 256, further comprising sealing the container, wherein the container is purged with nitrogen.

274. (original) The method of claim 256, further comprising sealing the container, wherein the container is sparged to eliminate oxygen.

275. (original) The method of claim 256, wherein the initial solution further comprises an isotonicity agent.

276. (original) The method of claim 275, wherein the isotonicity agent is sodium chloride.

277. (original) The method of claim 256, wherein the initial solution further comprising a cryoprotective agent.

278. (original) The method of claim 277 wherein the cryoprotective agent is a polyol.

279. (original) The method of claim 256, further comprising adding at least one opioid to the initial solution.

280. (original) The method of claim 279, wherein the opioid is selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol.

281. (original) The method of claim 279, wherein the opioid is solubilized in a nonaqueous solvent prior to addition to the initial solution.

282. (original) The method of claim 281, wherein the nonaqueous solvent is an oil, wax, or alcohol.

283. (original) A product comprising

a stable lyophilized formulation of methylnaltrexone, wherein the formulation upon reconstitution in water at a concentration of 20 mg/ml has a pH of between 2 and 6.

284. (canceled)

285. (original) The product of claim 283, wherein the formulation comprises a cryoprotecting agent present in an amount sufficient to render the formulation stable.

286. (canceled)

287. (original) The product of claim 285, wherein the cryoprotecting agent is a polyol.

288. (canceled)

289. (original) The product of claim 285, wherein the cryoprotecting agent is mannitol.

290. (canceled)

291. (Previously amended) The product of claim 283, further comprising any one or more of a buffering agent, a chelating agent and an antioxidant.

292. (canceled)

293. (Previously amended) A product comprising

a lyophilized formulation of methylnaltrexone prepared from a solution comprising the solution of claim 1.

294. (original) A product comprising

a lyophilized formulation of methylnaltrexone prepared from a solution comprising the solution of claim 36.

295. (canceled)

296. (Previously amended) A product comprising

a lyophilized formulation of methylnaltrexone prepared from a solution comprising the solution of claim 86.

297. (canceled)

298. (canceled)

299. (Previously amended) A product comprising

a lyophilized formulation of methylnaltrexone prepared from a solution comprising the solution of claim 136.

300. (canceled)

301. (canceled)

302. (original) A product comprising

methylnaltrexone and a degradation inhibiting agent selected from the group consisting of a chelating agent, a buffering agent, an anti-oxidant, and combinations thereof, wherein the degradation inhibiting agent is present in an amount sufficient to render stable a solution of the product containing a concentration of 20 mg/ml methylnaltrexone.

303. (original) The product of claim 302, wherein the product when in solution at a concentration of 20 mg/ml methylnaltrexone yields a solution with a pH of between 2 and 6.

304. (original) The product of claim 303, wherein the product has less than 1% methylnaltrexone degradation products when stored at room temperature in the solution for 6 months.

305. (canceled)

306. (canceled)

307. (original) A pharmaceutical preparation comprising methylnaltrexone;
sodium chloride,
citric acid,
trisodium citrate, and
disodium edetate.

308. (original) The pharmaceutical preparation of claim 307, wherein the preparation is a solution and the methylnaltrexone is present at between 20 and 40 mg/ml, the sodium chloride is present between 2 and 6 mg/ml, the citric acid is present between 0.05 and 0.1 mg/ml, the trisodium citrate is present between 0.025 and 0.075 mg/ml and the disodium edetate is present between 0.5 and 1.0 mg/ml.

309. (Previously amended) A kit comprising a package containing a sealed container comprising the pharmaceutical preparation of claim 231 and instructions for use.

310. (original) The kit of claim 309, further comprising a diluant container containing a pharmaceutically acceptable diluant.

311. (original) The kit of claim 310, further comprising instructions for mixing the preparation and diluant.

312. (original) The kit of claim 310, wherein the diluant is selected from the group consisting of a 5% dextrose solution and a physiological saline solution.

313. (original) The kit of claim 310, wherein the diluant is contained in a sealable bottle or an infusion bag.

314. (original) The kit of claim 309, further comprising an opioid container containing an opioid.

315. (original) The kit of claim 314, wherein the opioid is selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol.

316. (new) The pharmaceutical preparation of claim 231, wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA) or a derivative thereof.

317. (new) The pharmaceutical preparation of claim 316, wherein the derivative is dipotassium edetate, disodium edetate, edetate calcium disodium, sodium edetate, trisodium edetate, and potassium edetate.

318.(new) The pharmaceutical preparation of claim 317, wherein the EDTA or derivative thereof is present in a concentration from 0.001 to 100.0 mg/ml.

319.(new) The pharmaceutical preparation of claim 318, wherein the EDTA or derivative thereof is present in a concentration from 0.05 to 25.0 mg/ml.

320.(new) The pharmaceutical preparation of claim 319, wherein the EDTA or derivative thereof is present in a concentration from 0.1 to 2.5 mg/ml.

321. (new) The pharmaceutical preparation of any of claims 231, 316, 317, 318, 319 and 320, wherein the pH does not exceed 4.25.

322. (new) The pharmaceutical preparation of claim 321, wherein the pH is from 2.0 to 4.0.

323. (new) The pharmaceutical preparation of claim 322, wherein the pH is from 3.0 to 4.0.

324. (new) The pharmaceutical preparation of claim 323, wherein the pH is from 3.0 to 3.5.